

AWARD NUMBER: W81XWH-14-2-0191

TITLE: A Multicenter, Randomized Controlled Trial of Cerebrospinal Fluid Drainage in Acute Spinal Cord Injury

PRINCIPAL INVESTIGATOR: Nicholas Theodore, MD

CONTRACTING ORGANIZATION: Dignity Health
San Francisco, CA 94107-1773

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14. ABSTRACT The purpose of this randomized clinical trial is to evaluate the safety and efficacy of cerebrospinal fluid drainage (CSFD) and to provide a preliminary clinical efficacy evaluation of the combination of CSFD and elevation of mean arterial pressure (MAP) in patients with acute spinal cord injury. This study is currently screening and enrolling patients at all three active centers, which include Barrow Neurological Institute in Arizona, the University of Arizona in Tucson and the University of Alabama in Birmingham.					
15. SUBJECT TERMS acute spinal cord injury, cerebrospinal fluid drainage, mean arterial pressure, intrathecal pressure, improving neurologic motor outcomes, spinal trauma, traumatic injury					
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1. INTRODUCTION

In the United States, even though the incidence rate of acute spinal cord injury has been steadily dropping for several years, an estimated 10,000-14,000 people per year continue to suffer acute spinal cord injuries. These injuries incur significant costs to the patient and their families. This includes not only financial costs but also the serious psychological, physical and emotional tolls that are associated with this type of debilitating injury. A “cure” for spinal cord injury remains elusive despite efforts made by both industry, academia and charitable foundations. Most of the research funds that are currently being utilized to help patients suffering from spinal cord injury are being channeled to improving rehabilitation outcomes and not treating the injury itself in the immediate post-injury/trauma setting.

Improved long-term care technologies are being developed to help care for these patients both in the setting of professional rehabilitation centers as well as upon their return to their pre-injury settings. Even though these technological advances are invaluable to improving the lives of those living with spinal cord injuries – they do not tackle the problem of poor clinical outcomes immediately post-injury. In other words, they deal with the long-term consequences of the injury but not treating it in the acute setting. There is general consensus between experts that better outcomes are accomplished when treatment is provided as soon as possible following the injury. That was, and continues to be, at the core of this trial. Given the overall low prevalence rate of spinal cord injury, there is very limited industry funding supporting treatment research. Apart from a few trials looking at innovative methods of neural repair and regeneration there are few developments being made by the pharmaceutical and medical device industries in this field. The importance of federal funding to help support this research cannot be overstated.

The purpose of this ongoing randomized clinical trial is to evaluate the safety and efficacy of cerebrospinal fluid drainage (CSFD) and to provide a preliminary clinical efficacy evaluation of the combination of CSFD and elevation of mean arterial pressure (MAP) in patients with acute spinal cord injury. The basis behind this investigational method for treating acute spinal cord injury patients is the goal of reducing cell death and axonal damage immediately following injury. This is expected to lead to improved neurological function in the patients.

2. KEYWORDS

acute spinal cord injury, cerebrospinal fluid drainage, mean arterial pressure, intrathecal pressure, improving neurologic motor outcomes, spinal trauma, traumatic injury

3. ACCOMPLISHMENTS

What Were the Major Goals of the Project?

- *Prepare Research Protocol & Study Documents*
 - *Projected Completion: March 2015*
 - *Actual Completion: March 2015*
- *Contract the Sites and Vendors*
 - *Projected Completion: February 2015*
 - *Actual Completion: April 2016*
- *Obtain Regulatory Approvals*
 - *Initial Approvals*
 - *Projected Completion: March 2015*
 - *Actual Completion: February 2016*
 - *Continuing Approvals*
 - *Ongoing throughout study*

- Barrow Neurological Institute

Type of Event	Approval Date
Initial Submission	18-Sep-2014
Continuing Review	28-Jul-2015
Continuing Review	12-Jul-2016
Change in Research – ICF	13-Sep-2016
Other – HIPAA	13-Sep-2016
Change in Research – Change PI	19-Sep-2016

- University of Alabama

Type of Event	Approval Date
Initial Submission	01-Feb-2016
Change in Research - Amendment	20-Apr-2016
Continuing Review	15-Dec-2016

- University of Arizona

Type of Event	Approval Date
Initial Submission	25-Jun-2015
Change in Research – Protocol v2.0	20-Nov-2015
Change in Research – ICF	10-Feb-2016
Change in Research – Personnel Added	05-May-2016
Continuing Review	10-Jun-2016

- *Develop & Validate eCRF*
 - *Projected Completion: March 2015*
 - *Actual Completion: April 2015*
- *Program Clinical Data in SAS®*
 - *Projected Completion: February 2016*
 - *Actual Completion: July 2016*
- *Initiate Sites*
 - *Projected Completion: March 2015*
 - *Actual Completion: April 2016*
- *Enroll Subjects, Deliver Study Treatment, Perform Evaluations*
 - *Projected Completion: Per the current enrollment trends and the number of active sites – the study cannot be completed on time.*
 - *Actual Completion: Ongoing*

The table below shows the prescreening, screening and enrollment activities between January 2016 and January 2017 the prescreening, screening and enrollment statistics at all three participating sites:

Site Code	Organization	PI Name	Total Pre-screened	Total Screened	Total Enrolled
BNI	Barrow Neurosurgical Associates/ St. Joseph's Hospital	Udaya Kumar Kakaria, MD	55	2	2
UAT	University of Arizona	Michael Lemole, MD	79	2	2
UAB	University of Alabama, Birmingham	Mark N. Hadley, MD	8	0	0
		Total	142	4	4

- **Monitoring & Data Management**
 - *Projected Completion: Per the current enrollment trends and the number of active sites – the study cannot be completed on time.*
 - *Actual Completion: Ongoing throughout study*
- **Close the Study & Lock the Database**
 - *Projected Completion: January 2018*
 - *Actual Completion: Not Started, to be done following the completion of enrollment and final data cleaning/Source Data Verification/*
- **Analysis & Reporting**
 - *Projected Completion: Per the current enrollment trends and the number of active sites – the study cannot be completed on time.*
 - *Actual Completion: Not Started*

What Was Accomplished Under These Goals?

- **Prepare Research Protocol & Study Documents**
 - *The study documents were all completed and distributed to the sites on-time. This included, but was not limited to: The Source Worksheets (i.e. eCRFs), Clinical Study Protocol, Clinical Monitoring Plan, Study Reference Manual, Informed Consent Form template, Data and Coding Specifications, Programming guidelines, Site Initiation Visit Materials, delegation logs, etc.*
- **Contract the Sites and Vendors**
 - *Barrow Neurological Institute, University of Arizona, University of Alabama and Nor Consult (CRO) have fully executed Clinical Trial Agreements and/or Service Agreements in place. Barrow Neurological Institute is the neurotrauma facility where the Principal Investigator for this grant initiated the trail on behalf of the awardee, St. Joseph's Hospital. Barrow Neurological Institute is a subsidiary of St. Joseph's. The two other sites, University of Arizona and University of Alabama Birmingham are serving as independent enrollment centers for the purposes of this trial. The investigators at the sites, Dr. Lemole and Dr. Hadley, were listed as collaborating Principal Investigator in the approved grant application for this study. The CRO, Nor Consult, LLC is a Washington-based Limited Liability Company, whose contract with St. Joseph's Hospital was executed in 2014.*
- **Obtain Regulatory Approvals**
 - *Initial Approvals*

All of the participating centers have received an initial approval from their IRBs prior to engaging in any patient-centered study activities such as screening and enrollment. Per local guidelines, they have also received annual/continuing review renewals confirming that they may continue to perform study activities. In particular:

- *Barrow Neurological Institute has received initial and continuing IRB approval (annual renewal) for this study.*
- *University of Arizona has received initial and continuing IRB approval (annual renewal) for this study.*
- *University of Alabama has received initial and continuing IRB approval (annual renewal) for this study.*
- *Continuing Reviews / Amendments*
 - *All three sites are enrolling patients per version 2.0 of the Clinical Study Protocol.*
 - *University of Alabama has received IRB approval for a revised consent form.*
 - *University of Arizona has received approvals for English and Spanish consent forms.*
- *Develop & Validate eCRF*
 - *The Electronic Data Capture (EDC) system that is being utilized for this study has been developed and validated. It is continuously online, back-ups are created on a daily basis, and staff have been trained on data entry and query resolution. As new study staff are assigned to the study on the site-level, the CRO provides remote training to familiarize them with the specifics of the EDC and how to enter data. This may include study coordinators, data entry specialists, research administrators, etc.*
- *Initiate Sites*
 - *All Site Initiation Visits (SIV) have been completed.*
- *Monitoring & Data Management*
 - *Risk-based data checks (i.e. "edit checks") have been written and are actively supporting the ongoing data review activities. When an edit check fires, a CRA ensures that the site re-verifies or corrects the data. In addition, remote monitoring is conducted by the CRAs to confirm that the EDC entries correspond to source data. Finally, on-site visits are performed as the highest level of ensuring data integrity and overall compliance.*

What Opportunities for Training and Professional Development Has the Project Provided?

The Project has provided opportunities for the residents and fellows at all three enrollment centers to experience the clinical research process. In particular, they have been introduced to key tasks such as obtaining informed consent, pre-screening and screening activities, electronic data collection and safety evaluations/follow-up.

How Were the Results Disseminated to Communities of Interest?

Nothing to Report.

What Do You Plan to Do During the Next Reporting Period to Accomplish Goals?

During the next reporting period, we plan to continue pre-screening, screening and enrolling subjects at the three participating sites. Data management, data checks and on-site monitoring activities will continue to ensure the safety of the patients and the integrity of the data. The Investigators will convene to discuss possible solutions for the slower-than-anticipated enrollment of subjects into the trial. Annual IRB renewals will be obtained as needed to keep all three sites open-for-enrollment throughout the next reporting period.

Most importantly, the Principal Investigator and other grant collaborators will discuss changes in study operations, including scope and goal changes, with the DoD. By optimizing the way that the study is

conducted to better fit the realities of the actual number of eligible patients presenting – a more robust clinical determination will be achieved upon study conclusion.

4. IMPACT

What Was the Impact on The Development of The Principal Discipline(S) of the Project?

Nothing to Report.

What Was the Impact on Other Disciplines?

Nothing to Report.

What Was the Impact on Technology Transfer?

Nothing to Report.

What Was the Impact on Society Beyond Science and Technology?

Nothing to Report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change:

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them:

Following the initial of approval of this study by the DoD (i.e. the bestowing of the grant), we experienced a delay in actual study start-up activities due to the longer-than anticipated USAMRMC ORP HRPO Administrative Review process. Shortly thereafter, upon HRPO administrative review approval, there was a change made to the Clinical Study/Investigational Protocol (version 2.0). This included an update to the Informed Consent Form for the study, which had to be approved both locally on the site level as well as by the HRPO office. Upon completion of these administrative issues/delays - the screening and enrollment activities were put into action and resulted in the enrollment of the first subject in the trial.

As witnessed by the slower-than-anticipated enrollment and the lower-than-anticipated spinal cord injury cases presenting to the sites – the initial proposed study timelines are no longer viable. The sites had initially expected that a significantly higher number of patients eligible for the participation (according to the particulars of this study) would present to each site. Despite the very best efforts by all involved site staff, the sites have only been able to screen between 8-79 patients each, throughout the 2016 calendar year (8 at the University of Alabama Birmingham, 55 at Barrow Neurological Institute and 79 at the University of Arizona). Only four of these patients qualified for study treatment.

At the end of 2016 the Investigators and other involved experts reached out to the DoD to discuss potential changes in the study scope. This call is taking place in April 2017. The goal of this call is to brainstorm possible solutions that would ensure that the potential benefits of the study treatment are made available to more patients and that the study activities are harmonized with the overall goals and objectives of the goal to support a scientifically sound and clinically relevant deliverable.

The logistics surrounding the trial operations, in particular the enrollment and follow-up of the subjects, has proven to work and the staff at all three sites remain vigilant in screening their spinal cord trauma patients for possible inclusion in the study. The study procedure has proven to be capable of being successfully administered within the context of the trial, and the clinical data collection process for the study database is operationally sound.

Changes that had a significant impact on expenditures:

Nothing to Report. The study services completed until now were all delivered within the financial parameters of the study budget.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:

Nothing to Report. The protocol-prescribed procedures for this project remain unchanged.

6. PRODUCTS

Publications, conference papers, and presentation

Journal publications.

Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers, and presentations.

Nothing to Report.

Website(s) or another Internet site(s).

Nothing to Report.

Technologies or techniques.

Nothing to Report.

Inventions, patent applications, and/or licenses.

Nothing to Report.

Other Products.

Nothing to Report.

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	Nicholas Theodore, MD, no change
Name:	Nikolay Martirosyan, MD, no change
Name:	Bridget Dancs, no change
Name:	Anna McCann, no longer participating
Name:	Stan Abramov, no change
Name:	Veljko Kopjar, Project Manager, no change
Name:	Alexis Kosmin, Study Assistant, no longer participating
Name:	Wasinee Opal Sriapha, no longer participating
Name:	Samyukta Erabati, Associate Project Manager

Name: Michael Lemole, MD, no change
Name: Udaia Umar Kakaria, MD, PI at Barrow Neurological Institute
Name: Mark Hadley, MD, no change
Name: Christina Lo, Clinical Research Assistant
Name: Branko Kopjar, MD, PhD Statistician
Name: Dan Finan, Project Manager

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

On 19 September 2016 Dr. Kakaria took over the recruitment/enrollment responsibilities at Barrow Neurological Institute, with Dr. Nicholas Theodore retaining overall project oversight.

What other organizations were involved as partners?

Organization Name: University of Arizona, Tucson
Location of Organization: 1501 N. Campbell Ave, LSN 416 Bldg 221, Tucson, Arizona 85724
Partner's Contribution: Other (Investigational Site)

Organization Name: University of Alabama, Birmingham
Location of Organization: 510 20th Street South, FOT 1030, Birmingham, Alabama 35233
Partner's Contribution: Other (Investigational Site)

Organization Name: Nor Consult, LLC
Location of Organization: 677 Strander Blvd, Suite F, Seattle, WA 98188
Partner's Contribution: Other (Contract Research Organization)

8. Special Reporting Requirements

2017 Q1 (most recent) Quad Chart:

A multicenter, Randomized, Controlled, Trial of Cerebrospinal Fluid Drainage in Acute Spinal

Cord Injury

CDMRP Log Number: SC130237

Grants.gov ID Number: GRANT11501120

PI: Nicholas Theodore, MD

Org: St. Joseph's Hospital & Medical Center Award Amount: \$1,653,993

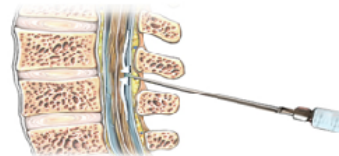


Study/Product Aim(s)

- The purpose of this RCT is to evaluate the safety and efficacy of cerebrospinal fluid drainage (CSFD) and to provide a preliminary clinical efficacy evaluation of combination of CSFD and elevation of Mean Arterial Pressure (MAP) in patients with acute spinal cord injury.

Approach

Subjects randomized to the Control Arm will receive elevation of MAP. Subjects randomized to the Experimental Arm will receive an intensive regime of CSFD and elevation of MAP. The duration of the study treatments will be 120 hours in both arms counting from the time when the study treatment has been initiated.



Accomplishments: During the first quarter of 2017, 49 spinal cord injury patients were prescreened for enrollment in this trial. 17 of these patients were prescreened at Barrow Neurological Institute, 23 at the University of Arizona and nine at the University of Alabama. Unfortunately, none of the patients qualified for inclusion in the trial.

Timeline and Cost

Activities	CY	14	15	16	17
Study Start Up					
Enrollment and Follow-up					
Enrollment and Follow-up					
Trial Termination and Analyses					
Estimated Budget (\$K)		504	310	308	339

Updated: April 19, 2017

Goals/Milestones

Quarter 1, 2017 –

Subject enrollment and follow-up, sites entering data, CRO monitoring study compliance (risk-based monitoring), CRO performing data reviews, issuing queries and working with sites to clean data on an ongoing basis, monitoring safety events.

Comments:

A meeting is being set up with the DoD scientific officer, study PI and support personnel to discuss ways of revising the study scope in order to offer more patients the potential benefit of joining this trial.

Budget Expenditure to Date

Approximate Projected Expenditure (direct costs): \$1, 206, 750

Actual Expenditure: \$801, 633.45

9. Appendices

None